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5

6 **NOVEL FORMULATIONS FOR THE**
7 **TRANSDERMAL ADMINISTRATION OF FENOLDOPAM**
8

9 **RELATED APPLICATIONS**

10 This application claims the benefit of U.S. Provisional Application Serial
11 No. 60/094,059, filed July 24, 1998.

12 **FIELD OF INVENTION**
13

14 This invention relates to sustained release formulations for the safe
15 and efficacious administration of fenoldopam for, among other things, the
16 treatment of hypertension, congestive heart failure, and acute and chronic
17 renal failure. More particularly, the invention relates to novel methods,
18 compositions, and devices for transdermally administering fenoldopam to a
19 subject through a body surface or membrane over a sustained time period.
20

21 **BACKGROUND OF THE INVENTION**
22

23 The transdermal route of parenteral delivery of drugs and other
24 biologically active agents ("agents") has been proposed for a wide variety of
25 systemically acting and locally acting agents on either a rate-controlled or
26 non-rate-controlled basis and is described in numerous technical publications
27 such as the following: U.S. Patent Nos. 3,598,122; 3,598,123; 3,731,683;
28 3,797,494; 4,031,894; 4,201,211; 4,286,592; 4,314,557; 4,379,454;
29 4,435,180; 4,559,222; 4,573,995; 4,588,580; 4,645,502; 4,698,062;
30 4,704,282; 4,725,272; 4,781,924; 4,788,062; 4,816,258; 4,849,226;
31 4,904,475; 4,908,027; 4,917,895; 4,938,759; 4,943,435; 5,004,610;
32 5,071,656; 5,122,382; 5,141,750; 5,284,660; 5,314,694; 5,342,623; and
33 5,635,203, the disclosures of which are incorporated in their entirety herein by
34 reference.

1 When first investigated in depth in the late 1960's, the transdermal
2 route of administration appeared to offer many advantages, particularly with
3 respect to agents that had short half lives and therefore required frequent,
4 repeated dosing or were subject to a high degree of first-pass metabolism by
5 the liver. The peaks and valleys in blood concentration resulting from
6 frequent periodic doses of short half-life agents would be eliminated and
7 replaced by substantially constant plasma concentration. This would not only
8 improve individual compliance but also would eliminate the alternating periods
9 of high side-effects and ineffective blood concentrations associated with
10 periodic dosing. Administering the agent through the skin directly into the
11 blood stream would also eliminate first-pass metabolism of orally administered
12 agents.

13 It was initially assumed, theoretically, that any short half-life agent of
14 high potency and skin permeability would be suitable for safe and effective
15 transdermal administration. This assumption, however, has not been proven
16 true.

17 The failure of the transdermal route to fulfill the initial expectations of its
18 potential as an administrative portal was primarily due to the incredible variety
19 of properties with which nature has endowed the skin to permit it to perform its
20 function as the primary barrier to prevent the ingress of foreign substances
21 into the body. See Transdermal Drug Delivery: Problems and Possibilities, B.
22 M. Knepp, et al, CRC Critical Reviews and Therapeutic Drug Carrier Systems,
23 Vol. 4, Issue 1 (1987) and Transdermal Delivery Systems: A Medical
24 Rationale, Gary W. Cleary, Topical Drug Bioavailability, Bioequivalence, and
25 Penetration, Plenum Press, 1993. Thus, the transdermal route of
26 administration, rather than being available to every short half-life agent of high
27 potency and skin permeability, was found to be available only to those few
28 agents that possess the proper combination of a host of characteristics, most
29 of which are unpredictable, required to render the agent suitable for safe and
30 effective transdermal administration.

31 The most significant of these characteristics are the following:

1 1. Skin Permeability. The permeability of the skin to the agent
2 must be sufficiently high so that the agent can be administered at a
3 therapeutically effective rate through an area of skin no greater than about
4 200 cm² and preferably no greater than 50 cm². The person-to-person
5 variation in skin permeability at similar sites should also be considered. U.S.
6 Patent Nos. 4,568,343, 4,746,515, 4,764,379, 4,863,738, 4,865,848,
7 4,888,354, 4,900,555, 5,378,730, 5,629,019, 5,641,504, 5,686,097, and WO
8 95/09006, WO 95/01167, WO 96/37231, and WO 96/40259 are related to
9 various compositions and methods for enhancing permeation of drugs through
10 the skin and are hereby incorporated in their entirety by reference.

11 2. Skin Binding. The skin beneath the transdermal delivery device
12 has the capability of creating a skin depot of drug by absorbing, adsorbing, or
13 binding a certain amount of agent. The amount of agent so bound must be
14 supplied to the skin before the agent can be delivered into the blood stream at
15 steady, therapeutically effective rates. If large amounts of the agent are
16 bound in the skin, significant delays in the onset of therapeutic effect ("lag
17 time") will be observed together with corresponding delays in termination of
18 effect upon removal of the device. The potential also exists for toxic
19 quantities of potent agents to be contained within the skin beneath the device.
20 Skin binding is not related to skin permeability. Agents that are highly
21 permeable may also be highly bound causing a lag time sufficiently long as to
22 render them unsuitable for their intended use.

23 3. Irritation. The skin reacts to many topically applied substances,
24 particularly those maintained under occlusion, by blistering or reddening
25 accompanied by unpleasant burning, itching, and stinging sensations. Animal
26 models are used to screen for irritation. Animal models, however, often
27 produce both false positives and false negatives. There is also a wide
28 interpersonal variation in susceptibility to irritation. An agent must be
29 minimally irritating in a large percentage of the target population in order to be
30 suitable for safe and effective transdermal administration. U.S. Patent Nos.
31 4,552,872, 4,756,710, 5,028,431, 5,130,139, 5,160,741, 5,304,379, and
32 5,451,407 are directed to overcoming problems of skin irritation associated

1 with transdermal drug delivery and are hereby incorporated in their entirety by
2 reference.

3 4. Sensitization. Sensitization is an allergic reaction which is
4 induced when an agent is first applied to the skin and is elicited upon
5 continued exposure which may occur immediately or after a long period of
6 seemingly harmless exposure.

7 The sensitization may be local, elicited by topical exposure,
8 which manifests itself as contact dermatitis accompanied by blistering, itching,
9 reddening and burning at the site of application. More seriously, the
10 sensitization may be systemic, elicited by topical application but manifesting
11 itself by more general allergic reactions at sites other than the site of
12 application. Most seriously, the systemic sensitization may be elicited by oral
13 or intravenous administration of the drug. If the latter occurs, the individual
14 will be unable to take the drug by any route of administration.

15 Animal models are used to screen for sensitization. Animal
16 models, however, produce both false positives and false negatives. There is
17 also a wide variation in the allergic reaction among individuals as well as
18 between sexes, races and skin types. It is obvious that a useful transdermal
19 agent must be minimally sensitizing in a large percentage of the target
20 population. U.S. Patent Nos. 5,000,956, 5,049,387, 5,120,145, and 5,149,539
21 are directed to overcoming sensitization problems associated with
22 transdermal drug delivery by the coadministration of a corticosteroid and are
23 hereby incorporated in their entirety by reference

24 5. Pharmacokinetic Properties. The half-life of an agent is the time
25 after administration that half of the amount administered has been eliminated
26 from the body. Because blood concentrations of continuously administered
27 agents continue to increase for approximately five half-lives before steady-
28 state constant blood concentrations are achieved, an agent must have a
29 relatively short half-life to be suitable for continuous transdermal
30 administration. The transdermal half-lives of most agents have not been
31 determined. When half-lives of agents determined from intravenous
32 administration are compared with half-lives determined from transdermal

1 administration, the transdermal half-lives are generally longer but there can be
2 wide variation in half-life between individuals based upon factors such as age,
3 sex, health, and body type.

4 6. Pharmacodynamic Properties. Constant blood levels may not
5 produce the desired therapeutic effects. For example, a therapeutic effect
6 may only be observed at peak blood concentration obtained from bolus
7 dosing but the peak blood or plasma concentration cannot be maintained
8 because of side effects associated therewith. Also, continuous administration
9 of many agents produces tolerance that may require either some agent-free
10 interval or continually increasing and therefore potentially hazardous doses of
11 the agent.

12 7. Potency. Although a certain degree of potency is required for
13 transdermally administered agent to be effective, it is also possible for an
14 agent to be too potent. As potency increases, lower blood concentrations are
15 required and much smaller quantities are administered. Because of normal
16 inter-individual variations and skin permeability, it may not be possible to
17 precisely control whether a individual is receiving 1 $\mu\text{g/hr}$ or 2 $\mu\text{g/hr}$, for
18 example. For a highly potent agent, a 1 $\mu\text{g/hr}$ administration may be totally
19 ineffective and a 2 $\mu\text{g/hr}$ rate fatal. Thus, the therapeutic index of an agent,
20 which is the ratio of toxic blood concentration to the therapeutic blood
21 concentration, becomes extremely significant. A highly potent agent should
22 also have a relatively wide therapeutic window in order to be suitable for
23 transdermal administration.

24 8. Metabolism. One of the perceived advantages of transdermal
25 administration was that it avoided the "first-pass" metabolism of the agent by
26 the liver that is associated with oral administration. It has now been
27 recognized, however, that the skin is also a large metabolizing organ in the
28 body for some drugs. Thus, although first-pass metabolism that occurs after
29 an orally administered agent enters the blood stream can be avoided, skin
30 metabolism, which occurs before the agent enters the bloodstream, cannot be
31 avoided. Skin metabolism is capable of creating metabolites that are inactive,

1 irritating, toxic, or comparable in biological activity to that of the agent. To be
2 suitable for transdermal administration, an agent must have metabolic
3 properties that are consistent with its therapeutic use on continuous
4 administration.

5 The above summarizes the primary characteristics that effect suitability
6 of an agent for transdermal administration that have been recognized to date.
7 There are undoubtedly others, some of which have not yet been recognized,
8 and, in order for an agent to be suitable for transdermal administration, it must
9 possess the right combination of all these characteristics, a combination of
10 which, as illustrated by the very few drugs that are now suitable for
11 administration from transdermal delivery devices, is quite rare and
12 unpredictable.

13 The present invention is directed to the transdermal administration of
14 fenoldopam, 6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenol)-1H-3-
15 benzapine-7,8 diol for the treatment of, among others, hypertension,
16 congestive heart failure, and acute and chronic renal failure. Fenoldopam
17 (Corlopam®) is a renal vasodilator DA₁ agonist that produces dose-dependent
18 reduction in systolic and diastolic blood pressure without producing clinically
19 significant increases in heart rate. The elimination half-life of fenoldopam is
20 about 5 minutes in mild to moderate hypertensive patients, with little
21 difference between the R (active) and S isomers. The preparation of
22 fenoldopam is described in U.S. Patent Nos. 4,197,297, 4,321,195, and
23 4,705,862, which are hereby incorporated in their entirety by reference.

24 Currently, fenoldopam is administered by infusion at a maximum rate of
25 up to 1.6 µg/kg min for periods of up to 48 hours. Oral administration does
26 not provide any clinical benefit, thus transdermal administration offers several
27 advantages. For example, transdermal administration of fenoldopam
28 significantly enhances patient compliance by alleviating the discomfort of
29 needles and cumbersome I.V. apparatus by providing a convenient dosage
30 form for once or twice weekly application. Other benefits discussed above
31 associated with the transdermal administration of fenoldopam are also
32 provided, such as sustained blood levels.

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DESCRIPTION OF TERMS

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5 As used herein, the term "fenoldopam" intends not only the basic form
6 of fenoldopam but also pharmaceutically acceptable salt forms of fenoldopam,
7 the R or S enantiomers of fenoldopam, either individually or as a racemic
8 mixture, and to mixtures thereof.

9 As used herein, the term "fenoldopam therapy" intends all medical
10 conditions for which fenoldopam is or will be indicated, including, without
11 limitation, for the treatment of hypertension, congestive heart failure, and
12 acute and chronic renal failure.

13 As used herein, the term "individual" intends a living mammal and
14 includes, without limitation, humans and other primates, livestock and sports
15 animals such as cattle, pigs and horses, and pets such as cats and dogs.

16 As used herein, the term "monoglyceride" refers to a monoglyceride or
17 mixture of monoglycerides of C₈-20 fatty acids and includes, without limitation,
18 glycerol monolaurate (GML), glycerol monooleate (GMO), glycerol
19 monocaprate (GMC), glycerol monocaprylate (GMCL), and glycerol
20 monolinoleate (GMLO).

21 As used herein, the term "permeation enhancement" intends an
22 increase in the permeability of skin to fenoldopam in the presence of a
23 permeation enhancer as compared to permeability of skin to fenoldopam in
24 the absence of a permeation enhancer.

25 As used herein, the term "permeation enhancer" intends an agent or a
26 mixture of agents which acts to increase the permeability of the skin to
27 fenoldopam.

28 As used herein, the term "permeation-enhancing amount" intends an
29 amount of a permeation enhancer which provides permeation enhancement
30 throughout a substantial portion of the administration period.

1 As used herein, the phrase "predetermined area of skin" intends a
2 defined area of intact unbroken skin or mucosal tissue. That area will usually
3 be in the range of about 5 cm² to about 100 cm².

4 As used herein the term "salt" intends, but is not limited to,
5 pharmaceutically acceptable organic or inorganic salts. Typical inorganic
6 salts include hydrogen halides such as hydrochlorides, carbonates,
7 phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates, and
8 sulfides. Organic salts include, but are not limited to, acid addition salts
9 including salts of monocarboxylic and polycarboxylic acids such as acetic
10 acid, malic acid, maleic acid, propionic acid, succinic acid, fumaric acid, citric
11 acid, benzoic acid, cinnamic acid, tartaric acid, and the like.

12 As used herein, the phrase "sustained time period" or "administration
13 period" intends at least about 8 hours and will typically intend a period in the
14 range of about one to about seven days.

15 As used herein, the term "therapeutically effective amount" intends the
16 dose of fenoldopam and/or its active metabolites that provides fenoldopam
17 therapy, in the case of adult and juvenile humans, the dosage range is about
18 1 - 20 mg fenoldopam per day.

19 As used herein, the term "therapeutically effective rate" intends a
20 delivery rate of fenoldopam and/or its active metabolites effective to achieve
21 therapeutic blood or plasma levels in an individual during the administration
22 period and is typically within the range of about 0.01 - 1.6 µg/kg/min.

23 As used herein, the term "therapeutic blood or plasma level" intends
24 the level of fenoldopam and/or its active metabolites in blood or plasma that
25 achieves a therapeutic effect for the desired fenoldopam therapy. For
26 individuals with mild to moderate malignant hypertension, this range is about
27 1 - 10 ng/mL.

28 As used herein, the term "transdermal" intends both percutaneous and
29 transmucosal administration, i.e., passage of fenoldopam through a body
30 surface or membrane such as intact unbroken skin or mucosal tissue into the
31 systemic circulation.

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4 SUMMARY OF THE INVENTION
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6 It is an aspect of this invention to provide sustained release
7 formulations to administer a therapeutically effective amount of fenoldopam
8 and/or its active metabolites, over an administration period.

9 More specifically, it is an aspect of this invention to provide
10 compositions and methods for the transdermal delivery of fenoldopam and/or
11 its active metabolites, and delivery systems for effecting the same, which are
12 suitable for the transdermal administration of fenoldopam and/or its active
13 metabolites continuously through a body surface or membrane at a
14 therapeutically effective rate in order to achieve and maintain therapeutic
15 blood or plasma levels in an individual.

16 Another aspect of this invention is to improve the compliance of
17 patients in need of fenoldopam therapy by providing compositions, devices,
18 and methods for the transdermal administration of fenoldopam at a
19 therapeutically effective rate.

20 According to this invention, it has been discovered that fenoldopam can
21 be safely and efficaciously administered transdermally at a therapeutically
22 effective rate to provide, among other things, treatment for hypertension,
23 congestive heart failure, and acute renal failure when coadministered with a
24 suitable permeation enhancer. Therefore, the invention comprises the
25 following aspects, either alone or in combination:

26 A composition of matter for the transdermal administration of
27 fenoldopam comprising an amount of fenoldopam and a permeation enhancer
28 in a carrier effective to permit sustained release of fenoldopam at a
29 therapeutically effective rate during an administration period in order to
30 administer a therapeutically effective amount of fenoldopam to achieve and
31 maintain therapeutic blood or plasma levels throughout a substantial portion
32 of the administration period.

1 A device for the transdermal administration of fenoldopam at a
2 therapeutically effective rate, comprising:
3 (a) a reservoir comprising fenoldopam and a permeation-
4 enhancing amount of a permeation enhancer;
5 (b) a backing behind the body contacting-distal surface of
6 the reservoir; and
7 (c) means for maintaining the reservoir in fenoldopam
8 transmitting relation with a body surface or membrane, wherein a
9 therapeutically effective amount of fenoldopam is delivered at a
10 therapeutically effective rate during an administration period in order to
11 achieve and maintain therapeutic blood or plasma levels throughout a
12 substantial portion of the administration period.

13 The permeation enhancer may be any permeation enhancer known in
14 the art to increase permeability of drugs through skin and includes, but is not
15 limited to, those disclosed in the above cited patents. Preferably, the
16 permeation enhancer comprises a permeation enhancing amount of a
17 permeation enhancer including, but not limited to monoglycerides, C₁₀ - C₂₀
18 fatty acid esters including ethyl palmitate and isopropyl myristate; acyl
19 lactylates such as caproyl lactic acid and lauroyl lactic acid; dimethyl
20 lauramide; dodecyl (lauryl) acetate; lactate esters such as lauryl lactate, and
21 myristyl lactate; monoalkyl ethers of polyethyleneglycol and their alkyl or aryl
22 carboxylic acid esters and carboxymethyl ethers such as polyethylene glycol-
23 4 lauryl ether (Laureth-4) and polyethylene glycol-2 lauryl ether (Laureth-2);
24 Myreth-3, myristyl sarcosine, and methyl laurate.

25 Additionally, the invention is directed to a method for treating an
26 individual suffering from hypertension, congestive heart failure, and/or acute
27 or chronic renal failure comprising transdermally administering fenoldopam to
28 the individual wherein a therapeutically effective amount of fenoldopam is
29 delivered at a therapeutically effective rate during an administration period in
30 order to achieve and maintain therapeutic blood or plasma levels of
31 fenoldopam throughout a substantial portion of the administration period.

1 These and other aspects of the present invention will be readily
2 apparent from the description and accompanying figures that follow.

3
4 BRIEF DESCRIPTION OF THE FIGURES

5
6 Figure 1 is a cross-section through a schematic perspective view of
7 one embodiment of a transdermal therapeutic system according to this
8 invention.

9 Figure 2 is a cross-section view through another embodiment of this
10 invention prior to application to the skin.

11 Figure 3 is a cross-section view through another embodiment of this
12 invention prior to application to the skin.

13 Figure 4 is a cross-section view through another embodiment of this
14 invention prior to application to the skin.

15 Figure 5 depicts the release rate of fenoldopam base from polymer
16 matrix formulations containing various permeation enhancers.

17 Figure 6 depicts the release rate of fenoldopam mesylate from polymer
18 matrix formulations containing various permeation enhancers.

19 Figures 7 and 8 depict the flux of fenoldopam base and mesylate from
20 polymer matrix formulations containing various permeation enhancers.

21 Figure 9 depicts the flux of fenoldopam base from polymer matrix
22 formulations containing GML and dodecyl acetate (lauryl acetate).

23
24 DETAILED DESCRIPTION OF THE INVENTION

25
26 According to this invention, it has been discovered that fenoldopam
27 can be safely and efficaciously administered by a sustained release
28 formulation. More specifically, it has been found that fenoldopam can be
29 safely and efficaciously administered transdermally at a therapeutically
30 effective rate to provide, among other things, treatment for hypertension,
31 congestive heart failure, and acute renal failure when coadministered with a
32 suitable permeation enhancer. The present invention provides novel

1 compositions, devices, and methods for fenoldopam therapy with improved
2 patient compliance to an individual in need of such therapy.

3 Therapeutic blood or plasma levels can be obtained from
4 administration rates in the range of 20 - 1500 $\mu\text{g/hr}$, preferably about 60 -
5 1000 $\mu\text{g/hr}$. Representative *in vitro* skin fluxes of fenoldopam through human
6 skin are in the range of about 5 $\text{ng/cm}^2 \cdot \text{hr}$ - 5.5 $\mu\text{g/cm}^2 \cdot \text{hr}$, depending on the
7 drug form, permeation enhancer, and adhesive.

8 This invention finds particular usefulness in administering fenoldopam
9 across skin. It is also useful, however, in administering fenoldopam across
10 mucosa. According to the invention, fenoldopam is placed in fenoldopam
11 transmitting relationship to an appropriate body surface, preferably in a
12 pharmaceutically acceptable carrier thereof, and maintained in place for the
13 desired administration period.

14 The fenoldopam and permeation enhancer are typically dispersed
15 within a physiologically compatible matrix or carrier, as more fully described
16 below, which may be applied directly to the body as an ointment, gel, cream,
17 suppository or sublingual or buccal tablet. When used in the form of a liquid,
18 ointment, lotion, cream or gel applied directly to the skin, it is preferable,
19 although not required, to occlude the site of administration. Such
20 compositions can also contain other permeation enhancers, stabilizers, dyes,
21 diluents, pigments, vehicles, inert fillers, anti-irritants, excipients, gelling
22 agents, vasoconstrictors, vasodilators, and other components of topical
23 compositions as are known to the art.

24 In other embodiments, fenoldopam would be administered from a
25 transdermal delivery device as more fully described below. Examples of
26 suitable transdermal delivery devices are illustrated in Figs. 1 - 4. In the
27 figures, the same reference numbers are used throughout the different figures
28 to designate the same or similar components. The figures are not drawn to
29 scale.

30 Referring now to Figure 1, a preferred embodiment of a transdermal
31 therapeutic system according to this invention comprises transdermal delivery

1 device 10 comprising a reservoir 12, preferably in the form of a matrix
2 containing fenoldopam, and a permeation enhancer dispersed therein.
3 Reservoir 12 is sandwiched between a backing 14 and an in-line contact
4 adhesive layer 16. The device 10 adheres to the surface of the skin 18 by
5 means of the adhesive layer 16. The adhesive layer 16 may optionally
6 contain the permeation enhancer and/or fenoldopam. A removable release
7 liner (not shown in FIG. 1) is normally provided along the exposed surface of
8 adhesive layer 16 and is removed prior to application of device 10 to the skin
9 18. Optionally, a rate-controlling membrane (not shown) may be present
10 between the reservoir 12 and the adhesive layer 16. Additionally, a non-rate
11 controlling tie layer membrane as disclosed in US Patent No. 5,635,203,
12 incorporated herein in its entirety by reference, may be present between the
13 reservoir 12 and adhesive 16 in any of the embodiments depicted in Figures
14 1- 4.

15 Although the preferred embodiments of this invention utilize an in-line
16 adhesive as is shown in Figure 1, other means for maintaining the system on
17 the skin can be employed. Such means include a peripheral ring of adhesive
18 outside the path of the drug from the system to the skin or the use of other
19 fastening means such as buckles, belts, and elastic arm bands.

20 Alternatively, reservoir 12 may be in the form of a matrix containing
21 fenoldopam and permeation enhancer dispersed within a suitable adhesive,
22 preferably a pressure sensitive adhesive. Such pressure sensitive adhesives
23 include, but are not limited to, polysiloxanes, polyacrylates, polyurethanes,
24 acrylic adhesives including cross linked or non-crosslinked acrylic
25 copolymers, vinyl acetate adhesives, ethylene vinylacetate copolymers, and
26 natural or synthetic rubbers including polybutadienes, polyisoprenes, and
27 polyisobutylene adhesives, and mixtures and graft copolymers thereof. The
28 matrix formulations according to this embodiment comprise the adhesive
29 containing fenoldopam and permeation enhancer, if present, laminated to a
30 backing on one surface and to a release liner on the other. In addition to the
31 fenoldopam and permeation enhancer, the matrix or carrier may also contain
32 dyes, pigments, inert fillers, anti-irritants, excipients and other conventional

1 components of pharmaceutical products or transdermal devices known to the
2 art. For example, the matrix may also be provided with hydrophilic water
3 absorbing and water soluble polymers known in the art such as polyvinyl
4 alcohol and polyvinyl pyrrolidone individually or in combination. Other suitable
5 water soluble and water absorbing polymers are known in the art, such as
6 those disclosed in U.S. Patent No. 5,176,916, hereby incorporated in its
7 entirety by reference.

8 Alternatively, as shown in FIG. 2, transdermal therapeutic device 20
9 may be attached to the skin or mucosa of a patient by means of an adhesive
10 overlay 22. Device 20 is comprised of reservoir 12 preferably in the form of a
11 matrix containing fenoldopam and a permeation enhancer dispersed therein.
12 A backing layer 14 is provided adjacent to one surface of reservoir 12.
13 Adhesive overlay 22 maintains the device on the skin and may be fabricated
14 together with, or provided separately from, the remaining elements of the
15 device. With certain formulations, the adhesive overlay 22 may be preferable
16 to the in-line contact adhesive 16 as shown in FIG. 1. Backing layer 14 is
17 preferably slightly larger than reservoir 12, and in this manner prevents the
18 materials in reservoir 12 from adversely interacting with the adhesive in
19 overlay 22. Optionally, a rate-controlling membrane (not shown in FIG. 2)
20 may be provided on the skin-proximal side of reservoir 12. A removable
21 release liner 24 is also provided with device 20 and is removed just prior to
22 application of device 20 to the skin.

23 In FIG. 3, transdermal delivery device 30 comprises a fenoldopam and
24 permeation enhancer reservoir ("fenoldopam reservoir") 12 substantially as
25 described with respect to FIG. 1. Permeation enhancer reservoir ("enhancer
26 reservoir") 26 comprises the permeation enhancer dispersed throughout and
27 contains fenoldopam at or below saturation, when in equilibrium with the
28 fenoldopam reservoir 12. Enhancer reservoir 26 is preferably made from
29 substantially the same matrix as is used to form fenoldopam reservoir 12. A
30 rate-controlling membrane 28 for controlling the release rate of the
31 permeation enhancer from enhancer reservoir 26 to fenoldopam reservoir 12
32 is placed between the two reservoirs. A rate-controlling membrane (not

1 shown in FIG. 3) for controlling the release rate of the enhancer and/or
2 fenoldopam from fenoldopam reservoir 12 to the skin may also optionally be
3 utilized and would be present between adhesive layer 16 and reservoir 12.

4 The rate-controlling membrane may be fabricated from permeable,
5 semipermeable or microporous materials which are known in the art to control
6 the rate of agents into and out of delivery devices and having a permeability to
7 the permeation enhancer lower than that of drug reservoir 12. Suitable
8 materials include, but are not limited to, polyethylene, polyvinyl acetate,
9 ethylene n-butyl acetate and ethylene vinyl acetate copolymers.

10 Superimposed over the permeation enhancer reservoir 26 of device 30
11 is a backing 14. On the skin-proximal side of reservoir 12 are an adhesive
12 layer 16 and a removable liner 24 which would be removed prior to application
13 of the device 30 to the skin.

14 In the embodiments of FIGS. 1, 2 and 3, the carrier or matrix material
15 of the reservoirs has sufficient viscosity to maintain its shape without oozing
16 or flowing. If, however, the matrix or carrier is a low-viscosity flowable
17 material such as a liquid or a gel, the composition can be fully enclosed in a
18 pouch or pocket, as known to the art from US Pat. No. 4,379,454 (noted
19 above), for example, and as illustrated in FIG. 4. Device 40 shown in FIG. 4
20 comprises a backing member 14 which serves as a protective cover for the
21 device, imparts structural support, and substantially keeps components in
22 device 40 from escaping the device. Device 40 also includes reservoir 12,
23 which contains the fenoldopam and permeation enhancer and bears on its
24 surface distant from backing member 14, a rate-controlling membrane 28 for
25 controlling the release of fenoldopam and/or permeation enhancer from
26 device 40. The outer edges of backing member 14 overlay the edges of
27 reservoir 12 and are joined along the perimeter with the outer edges of the
28 rate-controlling membrane 28 in a fluid-tight arrangement. This sealed
29 reservoir may be effected by pressure, fusion, adhesion, an adhesive applied
30 to the edges, or other methods known in the art. In this manner, reservoir 12
31 is contained wholly between backing member 14 and rate-controlling
32 membrane 28. On the skin-proximal side of rate-controlling membrane 28 are

1 an adhesive layer 16 and a removable liner 24 which would be removed prior
2 to application of the device 40 to the skin.

3 In an alternative embodiment of device 40 of FIG. 4, reservoir 12
4 contains the permeation enhancer and contains fenoldopam at or below
5 saturation. The fenoldopam and an additional amount of permeation
6 enhancer are present in adhesive layer 16, which acts as a separate
7 reservoir.

8 Fenoldopam can be administered to human skin or mucosa by direct
9 application to the skin or mucosa in the form of an ointment, gel, cream or
10 lotion, for example, but are preferably administered from a skin patch or other
11 known transdermal delivery device which contains a saturated or unsaturated
12 formulation of the fenoldopam and enhancer. The formulation may be
13 aqueous or non-aqueous. The formulation should be designed to deliver the
14 fenoldopam and any anti-irritant and/or enhancer at the necessary fluxes.
15 Aqueous formulations typically comprise water or water/ethanol and about 1-5
16 wt% of a gelling agent, an example being a hydrophilic polymer such as
17 hydroxyethylcellulose or hydroxypropylcellulose. When using aqueous
18 formulations, it is preferable to maintain the pH at less than about 5.5, more
19 preferably between about pH 2 - 4.5 in order to provide a stable fenoldopam
20 formulation. Typical non-aqueous gels are comprised of silicone fluid or
21 mineral oil. Mineral oil-based gels also typically contain 1-2 wt% of a gelling
22 agent such as colloidal silicon dioxide. The suitability of a particular gel
23 depends upon the compatibility of its constituents with the fenoldopam, anti-
24 irritant, and the permeation enhancer in addition to any other components in
25 the formulation.

26 The reservoir matrix should be compatible with fenoldopam, the
27 permeation enhancer, and any carrier therefor. The term "matrix" as used
28 herein refers to a well-mixed composite of ingredients. When using an
29 aqueous formulation, the reservoir matrix is preferably a hydrophilic polymer,
30 e.g., a hydrogel.

31 When using a non-aqueous formulation, the reservoir matrix is
32 preferably composed of a hydrophobic polymer. Suitable polymeric matrices

1 are well known in the transdermal drug delivery art, and examples are listed in
2 the above-named patents previously incorporated herein by reference. A
3 typical laminated system would consist essentially of a polymeric membrane
4 and/or matrix such as ethylene vinyl acetate (EVA) copolymers, such as those
5 described in US Pat. No. 4,144,317, preferably having a vinyl acetate (VA)
6 content in the range of from about 9% up to about 60% and more preferably
7 about 9% to 40% VA. Polyisobutylene/oil polymers containing from 4-25%
8 high molecular weight polyisobutylene and 20-81% low molecular weight
9 polyisobutylene with the balance being an oil such as mineral oil or
10 polybutene may also be used as the matrix material.

11 The amount of fenoldopam present in the therapeutic device and
12 required to achieve an effective therapeutic result depends on many factors,
13 such as the minimum necessary dosage of the fenoldopam for the particular
14 indication being treated; the solubility and permeability of the matrix, taking
15 into account the presence of permeation enhancer, of the adhesive layer and
16 of the rate-controlling membrane, if present; and the period of time for which
17 the device will be fixed to the skin. The minimum amount of fenoldopam is
18 determined by the requirement that sufficient quantities of fenoldopam must
19 be present in the device to maintain the desired rate of release over the given
20 period of application. The maximum amount for safety purposes is
21 determined by the requirement that the quantity of fenoldopam present must
22 not support a rate of release that reaches toxic levels.

23 The fenoldopam may be present in the matrix or carrier at a
24 concentration at or below saturation. An excess amount of fenoldopam above
25 saturation may be included in the matrix or carrier, the amount of excess
26 being a function of the desired length of the delivery period of the system.
27 Fenoldopam may be present at a level below saturation without departing
28 from this invention as long as it is continuously administered to the skin or
29 mucosal site at a therapeutic rate and for a period of time sufficient to deliver
30 a therapeutically effective amount of fenoldopam that provides the desired
31 therapeutic result.

1 The permeation enhancer useful in the present invention is selected
2 from those compounds which are compatible with fenoldopam and which
3 provide enhanced skin permeation to the drug when it is administered
4 together with the drug to the skin of a user. Additionally, the permeation
5 enhancer must not adversely interact with the adhesive of the in-line contact
6 adhesive layer if one is present. Examples of permeation enhancers are
7 disclosed in the patents cited above previously incorporated by reference and
8 can be selected from, but are not limited to, fatty acids, monoglycerides of
9 fatty acids such as glycerol monolaurate, glycerol monooleate, glycerol
10 monocaprate, glycerol monocaprylate, or glycerol monolinoleate; lactate
11 esters of fatty acids such as lauryl lactate, cetyl lactate, and myristyl lactate;
12 acyl lactylates such as caproyl lactic acid; esters of fatty acids having from
13 about 10 to about 20 carbon atoms, including, but not limited to, isopropyl
14 myristate, and ethyl palmitate; alkyl laurates such as methyl laurate; dimethyl
15 lauramide; lauryl acetate; monoalkyl ethers of polyethyleneglycol and their
16 alkyl or aryl carboxylic acid esters and carboxymethyl ethers such as
17 polyethylene glycol-4 lauryl ether (Laureth-4) and polyethylene glycol-2 lauryl
18 ether (Laureth-2); polyethylene glycol monolaurate; myristyl sarcosine;
19 Myreth-3; and lower C₁₋₄ alcohols such as isopropanol and ethanol, alone or
20 in combinations of one or more.

21 A preferred permeation enhancer according to this invention comprises
22 a monoglyceride of a fatty acid together with a suitable cosolvent, including,
23 but not limited to, lauryl acetate as disclosed in WO 96/40259 and esters of
24 C₁₀ - C₂₀ fatty acids such as lauryl lactate, ethyl palmitate, and methyl laurate.
25 Ethyl palmitate has been found to be particularly desirable as it is obtainable
26 at a high degree of purity, thus providing a purer and better defined
27 permeation enhancer and a system which is more readily characterized.
28 According to a particularly preferred embodiment, the permeation enhancer
29 comprises glycerol monolaurate (GML) and ethyl palmitate within the range of
30 1-25 wt% and 1-20 wt%, respectively, at a ratio of GML/ ethyl palmitate within
31 the range of 0.5 - 5.0, preferably 1.0 - 3.5. A particularly preferred
32 embodiment comprises 20 wt% GML and 12 wt% ethyl palmitate.

1 Another embodiment is directed to the use of surfactant sarcosines,
2 preferably myristyl sarcosine, as a permeation enhancer for pharmaceutically
3 acceptable salts of fenoldopam, preferably fenoldopam mesylate. In general,
4 formulations comprising fenoldopam base were found to be more permeable
5 through the skin as compared to formulations comprising pharmaceutically
6 acceptable salts of fenoldopam such as fenoldopam mesylate. However,
7 formulations comprising myristyl sarcosine as a permeation enhancer for
8 fenoldopam mesylate were found to exhibit higher transdermal fluxes than
9 formulations of the base. Additionally, fenoldopam mesylate when
10 administered transdermally did not exhibit the long lag period observed with
11 fenoldopam base. Thus, according to this embodiment, transdermal
12 compositions, devices, and methods are provided comprising a
13 pharmaceutically acceptable salt of fenoldopam, preferably fenoldopam
14 mesylate, together with a permeation enhancer for the fenoldopam salt,
15 preferably myristyl sarcosine, in order to transdermally administer fenoldopam
16 at therapeutically effective rates and lowered lag time. The use of other
17 surfactant sarcosines such as lauroyl sarcosine, sodium lauryl sarcosine,
18 cocoyl sarcosine, and oleoyl sarcosine are contemplated for use with the
19 compositions, devices, and methods according to this embodiment.

20 The permeation-enhancing mixture is dispersed through the matrix or
21 carrier, preferably at a concentration sufficient to provide permeation-
22 enhancing amounts of enhancer in the reservoir throughout the anticipated
23 administration period. Where there is an additional, separate permeation
24 enhancer matrix layer as well, as in FIGS. 3 and 4, the permeation enhancer
25 normally is present in the separate reservoir in excess of saturation.

26 According to another preferred embodiment, an anti-irritant is
27 dispersed throughout the matrix or carrier, preferably at a concentration
28 sufficient to deliver anti-irritant to the skin in an amount effective to reduce
29 skin irritation throughout the anticipated administration period. The anti-irritant
30 is preferably present in excess of saturation in order to ensure that the anti-
31 irritant is continuously administered with the fenoldopam and continues to be
32 present as long as any fenoldopam is present in the epidermis. Suitable anti-

1 irritants include, but are not limited to, methyl nicotinate as disclosed in US
2 Patent No. 5,451,407, corticosteroids, and buffering agents including ascorbic
3 acid and acetic acid. Such anti-irritants are known in the art as seen in the
4 above cited patents previously incorporated by reference.

5 For example, if a corticosteroid is used as the anti-irritant, it is
6 preferably administered at a flux within the range of 0.1 - 5.0 $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$.
7 Hydrocortisone is a preferred corticosteroid and is present in an amount of
8 about 1 - 5 wt%. The total amount of hydrocortisone administered is not to
9 exceed 5 mg / 24 hour in order to avoid possible systemic effects.
10 Hydrocortisone esters such as hydrocortisone acetate are also suitable. More
11 potent corticosteroids may not require a permeation enhancer as
12 hydrocortisone and hydrocortisone acetate do. However, the advantages of
13 hydrocortisone or its esters such as hydrocortisone acetate is that they are
14 approved for over-the-counter use. This invention contemplates the use of
15 any corticosteroid in addition to hydrocortisone and includes, without
16 limitation, beclomethasone, betamethasone, benzoid, betamethasone
17 dipropionate, betamethasone valerate, clobetasol propionate, clobetasol
18 butyrate, desonide, dexamethasone, fluocinonide, prednisolone, and
19 triamcinolone, for example.

20 Because of the wide variation in skin permeability from individual to
21 individual and from site to site on the same body, it may be preferable that the
22 fenoldopam, anti-irritant, and/or permeation enhancer, be administered from a
23 rate-controlled transdermal delivery device. Rate control can be obtained
24 either through a rate-controlling membrane as described in U.S. Patent No.
25 3,797,494 listed above, or through an adhesive or both as well as through
26 other means known in the art.

27 A certain amount of fenoldopam may bind reversibly to the skin, and it
28 is accordingly preferred that the skin-contacting layer of the device include
29 this amount of fenoldopam as a loading dose.

1 The surface area of the device of this invention can vary from about 1-
2 200 cm². A typical device, however, will have a surface area within the range
3 of about 5-60 cm², preferably about 20 cm².

4 The devices of this invention can be designed to deliver fenoldopam
5 effectively for an extended time period of from several hours up to 7 days or
6 longer. Seven days is generally the maximum time limit for application of a
7 single device because the adverse effects of occlusion of a skin site increases
8 with time and the normal cycle of sloughing and replacement of the skin cells
9 occurs in about 7 days.

10 Preferably, a device for the transdermal administration of fenoldopam,
11 at a therapeutically effective rate, comprises:

- 12 (a) a reservoir comprising:
13 (i) 1-50% by weight fenoldopam,
14 (ii) 1-50% by weight of a permeation enhancer,
15 (iii) 30 to 90% by weight of a polymeric carrier;
16 (b) a backing behind the skin-distal surface of the reservoir; and
17 (c) means for maintaining the reservoir in fenoldopam - transmitting
18 relation with the skin.

19 More preferably, a device for the transdermal administration of
20 fenoldopam, at a therapeutically effective rate, comprises:

- 21 (a) a reservoir comprising:
22 (i) 1 - 50% by weight fenoldopam,
23 (ii) 5 - 40% by weight of a permeation enhancer,
24 (iii) 30 - 90% by weight of a polymeric carrier;
25 (b) a backing behind the skin-distal surface of the reservoir; and
26 (c) means for maintaining the reservoir in fenoldopam- transmitting
27 relation with the skin.

28 Most preferably, a device for the transdermal administration of
29 fenoldopam, at a therapeutically effective rate, comprises:

- 30 (a) a reservoir comprising:
31 (i) 5 - 50% by weight fenoldopam,

- 1 (ii) 5 - 40% by weight of a permeation enhancer comprising a
2 monoglyceride and a fatty acid ester,
3 (iii) 30 - 90% by weight of a polymeric carrier;
4 (b) a backing behind the skin-distal surface of the reservoir; and
5 (c) means for maintaining the reservoir in fenoldopam - transmitting
6 relation with the skin.

7 The backing may be flexible or nonflexible and may be a breathable or
8 occlusive material. Suitable materials include, without limitation, polyethylene,
9 polyurethane, polyester, ethylene vinyl acetate, acrylonitrile, cellophane,
10 cellulose acetate, cellulosics, ethylcellulose, ethylene vinyl alcohol, plasticized
11 vinylacetate-vinylchloride copolymers, polyethylene terephthalate, nylons,
12 rayon, polypropylene, polyvinyl alcohol, polyvinyl chloride, metalized polyester
13 films, polyvinylidene chloride, polycarbonate, polystyrene, and aluminum foil.
14 The backing may be a multi-laminate film.

15 The means for maintaining the reservoir in drug and permeation
16 enhancer transmitting relation with the skin is preferably a pressure sensitive
17 adhesive including, but not limited to, polyisobutylene adhesives, silicone
18 adhesives, and acrylate adhesives known in the art including copolymers and
19 graft copolymers thereof. A further embodiment of the invention is directed to
20 including in the adhesive a small percentage, e.g., from about 1 to about 5
21 wt% of fenoldopam to assure an appropriate initial release rate.

22 The aforementioned patents describe a wide variety of materials which
23 can be used for fabricating various layers or components of the transdermal
24 fenoldopam delivery systems according to this invention. This invention,
25 therefore, contemplates the use of materials other than those specifically
26 disclosed herein including those which may become hereafter known to the
27 artist capable of performing the necessary functions.

28 The invention is also directed to a method of continuously
29 administering fenoldopam to a patient at a therapeutically effective rate over
30 an administration period in order to administer a therapeutically effective
31 amount and achieve and maintain therapeutic blood or plasma levels in a
32 patient.

1 A preferred embodiment of the present invention comprises a method
2 of treating acute or chronic renal failure. According to this embodiment, about
3 1 - 6 mg of fenoldopam, preferably 1.5 - 4 mg, most preferably 2 - 3 mg, are
4 delivered daily by the compositions, devices, and methods disclosed above.
5 To achieve this result, fenoldopam is delivered at a therapeutic rate within a
6 range of about 20 - 5500 $\mu\text{g/hr}$, preferably about 40 - 1500 $\mu\text{g/hr}$, most
7 preferably 60 - 600 $\mu\text{g/hr}$ from a reasonably sized transdermal delivery device
8 having a surface area of less than about 60 cm^2 for the treatment period,
9 usually about 6 hours to 5 days, preferably 24 - 72 hours.

10 The length of time of fenoldopam presence and the total amount of
11 fenoldopam in the plasma can be changed following the teachings of this
12 invention to provide different treatment regimens. Thus, they can be
13 controlled by the amount of time during which exogenous fenoldopam is
14 delivered transdermally to an individual or animal and the rate at which it is
15 administered.

16 Having thus generally described our invention, the following specific
17 examples describe preferred embodiments thereof but are not intended to
18 limit the invention in any manner.

19

20

EXAMPLE 1

21 About 3 grams of fenoldopam mesylate was weighed in a 250 ml
22 beaker and dissolved in 120 ml warm distilled water (or to a saturated
23 solution). 3M Na_2CO_3 solution was added to the fenoldopam solution drop by
24 drop until the solution reached pH 8.5. The whitened Na_2CO_3 solution
25 (converted fenoldopam base) was transferred to a Buchner funnel lined with
26 Whatman #1 filter paper, washed several times with distilled water and
27 vacuum dried at about 65 C. The dried fenoldopam base was transferred into
28 a tared vial and weighed.

29 Transdermal flux of fenoldopam base and mesylate was measured
30 from polymer matrices containing drug alone and from matrices containing
31 chemical permeation enhancers singly or in combination. Drug reservoirs

1 were prepared by mixing fenoldopam base or mesylate, ethylene vinylacetate
2 (EVA) (USI Chemicals, Illinois) having a vinyl acetate content of 40%, and
3 dodecyl acetate (DA) (Inoue Perfumery Mfg. Co. LTD, Tokyo, Japan), glycerol
4 monolaurate (GML) (Danisco Ingredients), polyvinyl pyrrolidone (PVP) (XL-10,
5 ISP Technologies, Inc., Calvert City, KY), lauramide diethanolamine (LDEA),
6 Laureth-2, Laureth-4, Myreth-3, myristyl sarcosine, glycerol monocaprates
7 (GMC), and/or caproyl lactic acid (CLA) (American Ingredient Co., Grand
8 Viejo, CA) in the amounts set forth in Table 1. The resulting mix was then
9 calendered to a 5 mil thickness between 2 release liners. The drug reservoir
10 was then heat laminated to a Medpar® backing on one surface and a 3M
11 acrylate adhesive on the other. Circular systems were cut with a stainless
12 steel punch.

Table 1
Fenoldopam Base and Mesylate Formulations

Formulation No.	Composition	Weight Percentages
1 (control)	fenoldopam base/EVA	15/85
2	fenoldopam base/EVA/GML/ML/PVP	15/37/20/12/16
3	fenoldopam base/EVA/Laureth-4	15/65/20
4	fenoldopam base/EVA/DML	15/65/20
5	fenoldopam base/EVA/MS	15/65/20
6	fenoldopam base/EVA/CLA/LDEA	15/50/20/15
7	fenoldopam base/EVA/Myreth-3	15/65/20
8	fenoldopam base/EVA/Laureth-2	15/65/20
9	fenoldopam base/EVA/GMC	15/65/20
10	fenoldopam mesylate/EVA	15/85
11	fenoldopam mesylate /EVA/GML/ML/PVP	15/37/20/12/16
12	fenoldopam mesylate /EVA/Laureth-4	15/65/20
13	fenoldopam mesylate /EVA/DML	15/65/20
14	fenoldopam mesylate /EVA/MS	15/65/20
15	fenoldopam mesylate /EVA/CLA/LDEA	15/50/20/15
16	fenoldopam mesylate /EVA/Myreth-3	15/65/20
17	fenoldopam mesylate /EVA/Laureth-2	15/65/20
18	fenoldopam mesylate /EVA/GMC	15/65/20

Release of fenoldopam from transdermal systems into aqueous medium was measured over 24 hours at 35° C. The release liner of the matrix system was then removed and each system had its exposed edges masked. The systems were then mounted on a Teflon® holder of a release rate rod using nylon mesh and nickel wire. A known volume of receptor solution (30 ml 0.01M phosphate buffer solution at pH 2.5) was then placed in a test tube and equilibrated at 35°C. The test tube was placed in a water bath and maintained at 35°C. The Teflon rod with attached system was then reciprocated within the test tube by attaching the rod to a motor which caused constant vertical mixing.

At given time intervals, the entire receptor solution was removed from the test tubes and replaced with an equal volume of fresh receptor solutions

1 previously equilibrated at 35°C. The receptor solutions were stored in capped
2 vials at 4 °C until assayed for fenoldopam content by HPLC. From the drug
3 concentration and the volume of the receptor solutions, the area of the system
4 and the time interval, the release rate of the drug from the system was
5 calculated as follows: (drug concentration X volume of receptor)/(area x time)
6 = release rate ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$). Release rates for the fenoldopam base and
7 mesylate formulations are depicted in Figures 5 and 6, respectively.

8

9

EXAMPLE 2

10

11 Transdermal systems set forth in Table 1 were prepared according to
12 Example 1 and used to measure permeation through human cadaver skin.
13 Circular pieces of heat stripped human epidermis were blotted dry just prior to
14 use and the stratum corneum surface of the epidermis was applied to the
15 fenoldopam releasing side of the system. The edges of epidermis were then
16 folded around the system so that none of the system edge was exposed to
17 the receptor solution. Fenoldopam permeation through the epidermis was
18 then measured according to the procedure set forth in Example 1. The
19 receptor compartment was filled with a known volume of 0.01 M
20 $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ which was adjusted to pH 2.5 with 10% H_3PO_4 buffer
21 solution previously equilibrated at 35 °C. Figures 7 and 8 depict the *in vitro*
22 transdermal flux of fenoldopam through human epidermis with various
23 permeation enhancers.

24

EXAMPLE 3

25

26 Transdermal systems set forth in Table 2 were prepared according to
27 the procedure set forth in Example 1 and used to measure permeation
28 through human cadaver skin. Circular pieces of heat stripped human
29 epidermis were blotted dry just prior to use and the stratum corneum surface
30 of the epidermis was applied to the fenoldopam releasing side of the system.
31 The edges of epidermis were then folded around the system so that none of

1 the system edge was exposed to the receptor solution. Fenoldopam
 2 permeation through the epidermis was then measured according to the
 3 procedure set forth in Example 1. The receptor compartment was filled with a
 4 known volume of 0.01 M $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ which was adjusted to pH 2.5 with
 5 10% H_3PO_4 buffer solution previously equilibrated at 35 °C. Figure 9 depicts
 6 the mean in vitro transdermal flux of fenoldopam through human epidermis
 7 with various permeation enhancers.

8 Table 2

9 Fenoldopam Base Formulations

Formulation No.	Composition	Weight Percentages
1 (control)	fenoldopam base/EVA	15/85
2	fenoldopam base/EVA/GML/DA	15/53/20/12

10

11 Having thus generally described our invention and described certain
 12 specific embodiments thereof, including the embodiments that applicants
 13 consider the best mode of practicing their invention, it should be readily
 14 apparent that various modifications to the invention may be made by workers
 15 skilled in the art without departing from the scope of this invention which is
 16 limited only by the following claims.